Remarks

Applicants thank the Examiner for kindly extending Applicants, David Wolf and Dylan Bulseco, and their representative, Allison Johnson, the courtesy of a telephone interview on Tuesday, October 3, 2006. The deficiencies of the Rigler et al. reference, including its failure to teach a sample composition that includes a pathogen, were discussed. No agreement was reached.

Claims 59, 60, 62, 65, 66 and 68 have been amended, claims 67 and 69 have been cancelled and new claims 118-138 have been added. Support for the amendments to the claims and the new claims can be found in general throughout Applicant's Specification, and in particular, for example, as follows: claim 59 and 60, page 8, lines 21-28, claims 118 and 138, original claim 62, claims 119 and 122, page 4, lines 3-4, claims 120, 121 and 123, page 32, lines 24-25 and 29-30, claims 124-129, page 37, lines 27-30, claim 130, original claims 65 and 66, claims 131 and 132, page 31, lines 27, claims 132 and 133, Examples 1-4 and FIGS. 1A, 2A 3A and 4A, claims 134 and 135, FIG. 4A, claims 136 and 137, FIGS. 1A and 2A. No new matter has been added. Applicants reserve the right to prosecute the claims in their original form in a continuing application.

Applicants thank the Examiner for kindly rejoining Group III, claims 70-73, to the set of claims currently under prosecution, i.e., Group II.

Applicants note that in their April 21, 2006 Response to Restriction Requirement they elected to prosecute all of the claims of Group II, including claim 68, elected pathogen as the species of Paragraph 13 of the March 21st Office action and further stated that claims 59-69 read on the elected species of pathogen (see, April 21, 2006 Response to Restriction Requirement, page 20). Accordingly, Applicants are confused by the Examiner's decision to withdraw claim 68 from further consideration. Applicants respectfully traverse the withdrawal of claim 68 from prosecution and respectfully request that it remain in prosecution.

Applicants also respectfully traverse the Examiner's characterization of the earliest filing date to which the above-captioned application is entitled. Applicants submit that the above-captioned application, as a whole, is entitled to the benefit of the earlier filing dates of U.S. 60/400,503, i.e., August 1, 2002, and U.S. 60/461,394, i.e., April 8, 2003, for everything disclosed in those applications. The test for determining

whether a claim is entitled to the benefit of an earlier filed application is whether the disclosure of the prior-filed application provides adequate support and enablement for the claimed subject matter of the later filed application in compliance with the requirements of 35 U.S.C. § 112, first paragraph (see M.P.E.P. 201.11). (Emphasis added.) The July 21st Office action does not specify the numbers of the claims that do not satisfy the requirements of 35 U.S.C. § 112, first paragraph. Applicants agree that the claims currently under prosecution, i.e., the claims that have not been withdrawn or cancelled, are entitled to a filing date at least as early as December 2, 2002. However, Applicants disagree that the application as a whole is not entitled to the benefit of the earlier filing dates of U.S. 60/400,503, i.e., August 1, 2002, and U.S. 60/461,394, i.e., April 8, 2003. Accordingly, Applicants traverse the Examiner's determination to the extent that it extends to the application as a whole and view the Examiner's determination as being limited to the specific claims under prosecution and not claims that have been withdrawn or cancelled.

Regarding the June 9, 2004 Information Disclosure Statement, Applicants thank the Examiner for noting that the International Preliminary Examination Report (IPER) does not include a publication year. The IPER is not prior art to the above-captioned application; it was submitted to provide the Examiner with information as to the corresponding application in the PCT.

Applicants also note that there is no indication that references AB-AE on substitute Form 1449 submitted February 3, 2004, were reviewed by the Examiner. Applicants respectfully request that the Examiner indicate his review by initialing the substitute Form 1449 and forwarding a copy of the same to Applicants at the correspondence address of record. A copy of the relevant page from the substitute Form 1449 is attached hereto to facilitate the Examiner's review.

Claims 59-69 stand rejected under 35 U.S.C. § 112, second paragraph.

Applicants submit that the step of "determining the presence or absence of the pathogen" is not a necessary step for the method of claim 59. Rather, the method can only include the recited steps and still be a useful method. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Applicants submit that the amendments to claims 59 and 60 pertaining to the sample and the excited subvolume render moot the outstanding rejection thereto under 35 U.S.C. § 112, second paragraph.

Regarding amended claim 60 and the recitation, "a predetermined pathogen," Applicants submit that the term "predetermined" means determined in advance. The probe of amended claim 60 is of such a nature that it is known to bind to a known pathogen. In other words, in advance of conducting the method, it has been determined (e.g., through scientific means) that the probe will bind a certain pathogen. Thus, the use of the term "predetermined" in amended claim 60 does not cause the limitation of claim 60 to read on a mental step. In light of the above, the skilled artisan upon reading claim 60 would readily understand what is meant by the phrase "a predetermined pathogen." Applicants submit, therefore, that claim 60 satisfies the criteria of 35 U.S.C. § 112, second paragraph, and respectfully request that the rejection be withdrawn.

Applicants submit that the amendments to claims 60 and 69 render moot the rejections of claims 63 and 69 under 35 U.S.C. § 112, second paragraph, and respectfully request that they be withdrawn.

Claims 59-67 and 69 stand rejected under 35 U.S.C. § 102(e) over Rigler et al. (US 6,582,903 B1).

Rigler et al. disclose a method for identifying one or a small number of molecules in very small volumes (i.e., 10^{-14} to 10^{-17} liters) using a laser excited fluorescence correlation spectroscopy. Rigler et al. are particularly interested in studying the interactions that occur between molecules at the molecular level including biochemical reactions, equilibrium constants and rate constants of single molecules (Rigler et al., col. 5, lines 22-26). A very small measuring volume is important to Rigler et al. because it allows for the dwell time of a molecule in the measuring volume to be about 1000 times shorter than in conventional systems and thereby enables equilibrium constants and rate constants of specific biological recognition reactions to be measured (*Id.* at lines 47-55). Rigler et al. explain that problems in the art include the fact that the observation element was so large that biologically interesting molecules having low translational diffusion coefficients were present in the observation element for a period of about 50 ms (*Id.* col. 3, lines 3-5). Such a period, according to Rigler et al., is significantly too large since it

causes strong bleaching of the respective dye ligands serving as the luminophore (*Id.* at lines 5-7). The Rigler et al. method relies on frequent excitation of the luminophore. According to Rigler et al., frequent excitation increases the chemical reactivity of the luminophorous structure towards molecules of the environment, in particular oxygen, whereby the luminescence is altered or quenched (*Id.* at lines 7-11). Rigler et al. further explain that photobleaching leads to false measuring data (*Id.* at lines 11-14). Rigler et al. also disclose that the measuring period over which their analysis is conducted is no greater than 500 milliseconds (see *Id.*, Abstract). Rigler et al. go on to explain that for slowly diffusing complexes such as cell cultures or tissues, the translational diffusion of the complexes is irrelevant for the analysis (*Id.*, col. 21, lines 56-62). In other words, the complex appears as if it is stationary, i.e., it is effectively stationary, for purposes of the Rigler et al. analysis.

Claim 59 is now directed to a method of assaying for a pathogen that includes exciting a sample with radiation, the sample including a least one pathogen, at least one probe, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the exited sample and analyzing the fluctuations of the fluorescence due to diffusion or flow of the pathogen through the subvolume. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. 2131. Rigler et al. disclose a method of identifying a molecule using laser excited fluorescence correlation spectroscopy in which the measurements are performed in small volume units. Specifically, Rigler et al. disclose that critical aspect of the method is the introduction of ultra small measuring volumes (see, Rigler et at., col. 3, lines 21-24, and col. 3, lines 46-54). Rigler et al. do not disclose a method of assaying for a pathogen in a sample. Rigler et al. also do not disclose a sample volume that includes at least one pathogen, as required by claim 59. The July 21, 2006 Office action does not dispute this. The July 21st Office action refers to "pathogen components" (not pathogens) and asserts that the passage at column 16, line 47 teaches detecting pathogens. A careful reading of the cited passage, however, reveals that it actually discloses that the method disclosed by Rigler et al. can be used to solve the problem of finding, characterizing and optionally isolating "the pharmacologically important target molecule of a known active substance. . . . search for and distinction

[*sic*] between different receptor molecules, preferably in distinguishable biological targets (....tumor/non-tumor, pathological/non-pathological...)." Rigler et al., col. 16, lines 29-47. (Emphasis added.) A molecule is not a pathogen. A pathogen is an organism. In addition, a pathogen is an agent that causes a disease state. The above-quoted passage refers to studying interactions between target molecules and receptor molecules. It does not teach a method of assaying for a pathogen in a sample. The above-quoted passage also does not teach a sample volume that includes a pathogen, as required by claim 59. Rather, it refers to molecules, characterizing and optionally isolating molecules that are the targets of known pharmacologically active substances, and searching for and distinguishing between different receptor molecules in "distinguishable biological targets". Nothing in the cited passage teaches a sample volume that includes a pathogen --let alone a pathogen, a probe and a fluorescent tag.

The disclosure in Rigler et al. at column 8, lines 25-30 also fails to teach the method of claim 59. The cited passage discusses the fact that the method of Rigler et al. is applicable to DNA/RNA analysis and that in such genetic analyses (including the DNA/RNA analysis used in the determination of infective pathogens), the sensitivity of the diagnostic method is often critical. Rigler et al. discuss DNA/RNA analysis in further detail at column 35, line 66-column 36, line 64.

The July 21st Office action asserts that the passage at column 25, lines 10-25 of Rigler et al. teaches pathogens that include a bacteria or virus. The cited passage does not, however, teach a method of assaying for a pathogen in a sample or a sample that includes a pathogen, rather the cited passage refers enriching nucleic acids of viruses or bacteria by hybridization.

The July 21st Office action asserts that the passage at column 35, lines 57-65 of Rigler et al. teaches pathogens that include a bacteria or virus. The cited passage discloses,

> The sensitivity of the detection of viral or bacterial pathogens in the gas phase (air germs) or in solutions or suspensions in small sample volumes, as are sufficient of the detection according to the invention can be increased by using simple filtration steps. They can be extracted from larger volumes through filters or filter systems and incorporated in small sample volumes.

This passage is in the midst of a three column discussion regarding DNA/RNA analysis. The passage relates to Rigler et al.'s earlier statements that it the sensitivity of genetic analysis methods for determining of infective pathogens is often critical (see *Id.*, col. 8, lines 25-28). The passage does not expressly teach a sample that includes a pathogen, a probe and a fluorescent tag. Moreover, nothing in Rigler et al. teaches the skilled artisan how to assay for the presence of a pathogen in a sample. Rather, the discussion surrounding this passage and the corresponding examples related thereto refer to analyzing DNA and RNA. This is further demonstrated by the Example section wherein DNA is analyzed. Rigler et al. thus fail to teach a required element of the method of claim 59, i.e., a sample volume that includes a pathogen. Applicants submit, therefore, that the rejection of claim 59 under 35 U.S.C. § 102(e) over Rigler et al. is unwarranted and respectfully request that it be withdrawn.

Claim 60 is now directed to a method of assaying for the presence of a pathogen in a sample where the method includes exciting a sample with radiation, the sample including at least one probe capable of binding a predetermined pathogen, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence that are due to the diffusion or flow of the pathogen through the subvolume, and determining the presence or absence of the pathogen. Rigler et al. do not teach a method of assaying for the presence of a pathogen. Rather Rigler et al. seek to obtain information about molecules. Rigler et al. also do not analyze fluctuations in fluorescence due to the diffusion or flow of a pathogen through a sample volume. To the contrary, Rigler et al. seek to obtain information about interactions between molecules. In particular, Rigler et al. look for information about equilibrium constants, dissociation rate constants of complexes, and conformational changes in biological macromolecules and the related thermodynamic and kinetic constants. Rigler et al. obtain this information by using an ultra small measuring volume and analyzing the interaction of molecules while they are in that volume through the translational or rotational diffusion of the molecules. Rigler et al. excite the same molecule thousands of times while it is in the sample volume. This is necessary in order for Rigler et al. to observe the molecular interactions in which they are interested. Rigler et al. also disclose that the average diffusion times of smaller molecules, molecular

complexes or molecular fragments through the measuring volume must be sufficiently small or they will be destroyed by exposure to the excitation radiation. In particular, Rigler et al. explain that the dwell time of the luminophore in the measuring volume must be sufficiently short or photobleaching will occur. Rigler et al. do not teach, and are not interested in, analyzing fluctuations in fluorescence due to diffusion or flow of an organism such as a pathogen through a subvolume. Rigler et al. expressly disclose that the translational diffusion of larger complexes such as cell cultures and tissues is irrelevant for their analysis, which relies on molecular interactions (Rigler et al., col. 21, lines 56-62). In other words, cell cultures and tissues appear as if they are stationary, i.e., they are effectively stationary, for purposes of the Rigler et al. analysis. Moreover, Rigler et al. have intentionally designed their method to render the diffusion of larger complexes such as cell cultures and tissues irrelevant. Again, Rigler et al. have done so because they are interested in the molecular interactions that are occurring in or on the cell or tissue --not the movement of the cell or tissue through the measurement volume. For at least these reasons, Applicants submit that Rigler et al. do not teach the method of claim 60. Accordingly, the rejection of claim 60 under 35 U.S.C. § 102(e) over Rigler et al. has been overcome and Applicants respectfully request that it be withdrawn.

Claims 61-66 are distinguishable under 35 U.S.C. § 102(e) over Rigler et al. for at least the same reasons as set forth above in distinguishing claim 60.

Claims 59-64 and 66 stand rejected under 35 U.S.C. § 102(b) over Rigler (Journal of Biotechnology, vol. 41 (1995), pp. 177-186).

Rigler discloses methods for analyzing molecular interactions between ligands and target molecules by exciting a sample to fluorescence with a laser beam and correlating the fluctuations of molecular intensity. Rigler describes the detection of a typical biological interaction of a fluorescence labeled DNA primer of 18 nucleotides binding to a target DNA molecule, namely single stranded M13 bacteriophage DNA.

Claim 59 is directed to a method of assaying for a pathogen in a sample where the sample includes a least one pathogen, at least one probe, and at least one fluorescent tag. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. 2131. Rigler discloses a method of examining molecular interactions using fluorescence

correlation spectroscopy. Specifically, the method includes exciting a small volume of a sample that includes a molecule (see, Rigler, page 177). None of the actual methods disclosed in Rigler include a sample that includes a pathogen. In addition, Rigler does not teach a method of assaying for a pathogen in a sample where the sample includes a pathogen. Nothing in the record establishes anything to the contrary. Rigler also does not teach how to assay for a pathogen in a sample. Rather, Rigler finds biologically important interactions to be the binding of a fluorescence labeled DNA primer of 18 nucleotides to a target DNA. Rigler analyzes the interaction by the difference in diffusion times of the free and DNA-bound primer. Rigler further discloses determining the equilibrium constants, association and dissociation rate constants and details of the reaction mechanism between low molecular weight acetylcholine, alpha-bungarotoxin, and high molecular weight acetylcholine receptor. Rigler also discloses that single virus molecules containing RNA or DNA sequences can be made visible by incorporating fluorescence markers in a specific way. Rigler goes on to disclose that this can be achieved by hybridization of DNA or RNA with fluorescence labeled primers or by replication of the vital DNA/RNA with fluorescence labeled nucleotides and unlabelled specific primer. Rigler further discloses, "The development outlined above seems not only to be promising for detecting nucleic acid sequences of infectious and pathogenic agents." Rigler, page 184. (Emphasis added.) Nucleic acid sequences are not pathogens. In addition, the "development" referred to by Rigler involves detecting molecules –not pathogens. Therefore, the above-quoted statement is of no moment to the method of claim 59. Since Rigler does not teach a method of assaying for the presence of a pathogen or a sample volume that includes a pathogen, Rigler fails to teach a required element of the method of claim 59. Applicants submit, therefore, that the rejection of claim 59 under 35 U.S.C. § 102(b) over Rigler is unwarranted and respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that the next action indicate, by reference to page and line number, the location in Rigler of a teaching of a sample that includes a pathogen.

Claim 60 is now directed to a method of assaying for the presence of a pathogen in a sample, the method including exciting a sample with radiation, the sample including at least one probe capable of binding a predetermined pathogen, and at least one

fluorescent tag, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence that are due to the diffusion or flow of the pathogen, and determining the presence or absence of the pathogen. Rigler does not teach assaying for the presence of a pathogen in a sample. Rather Rigler describes analyzing interactions of molecules with DNA and RNA. The DNA and RNA of Rigler are not pathogens. Applicants submit, therefore, that the rejection of claim 60 under 35 U.S.C. § 102(b) over Rigler has been overcome and respectfully request that it be withdrawn.

Claims 61-64 and 66 are distinguishable under 35 U.S.C. § 102(b) over Rigler for at least the same reasons as set forth above in distinguishing claim 60.

Claims 59-61 and 66 stand rejected under 35 U.S.C. § 102(b) over Weiner et al. (Digestion, 2000, vol. 61, pp. 84-89).

Weiner et al. disclose methods for combining an amplification technique, namely the PCR, with fluorescence correlation spectroscopy to quantify levels of pathogenic hepatitis C virus RNA in clinical samples. More specifically, Weiner et al. describe extracting HCV RNA from human serum, and performing cDNA synthesis and PCR using a Cy3-labeled fluorescent probe to HCV RNA. Weiner et al. also disclose diluting the PCR mixtures, denaturing the mixtures to resolve nonspecific binding of the fluorescence-labeled probes, and analyzing the crude PCR mixtures with an argon-ion laser fluorescence correlation spectrometer to determine the amount of fluorescence-labeled nucleic acids for identification of the virus.

Claim 59 is now directed to a method of assaying for a pathogen in a sample where the sample includes a least one pathogen, at least one probe, and at least one fluorescent tag. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. 2131. Weiner et al. disclose a method of using fluorescence correlation spectroscopy to measure levels of hepatitis C virus RNA, which is a macromolecule. The RNA of hepatitis C virus is not a pathogen. Therefore, Weiner et al. do not teach a sample that includes a pathogen. Nothing in the record establishes anything to the contrary. Weiner et al. thus fail to teach a required element of the method of claim 59. Applicants submit, therefore, that the rejection of claim 59 under 35 U.S.C. § 102(b) over Weiner et al. is unwarranted and respectfully request that it be withdrawn. Should this

rejection be maintained, Applicants respectfully request that the next action indicate, by reference to page and line number, the location in Weiner et al. of a teaching of a sample that includes a pathogen.

Claim 60 is now directed to a method of assaying for the presence of a pathogen in a sample where the method includes exciting a sample with radiation, the sample including at least one probe capable of binding a predetermined pathogen, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence that are due to the diffusion or flow of the pathogen through the subvolume, and determining the presence or absence of the pathogen. Weiner et al. do not teach a method of assaying for the presence of a pathogen. Rather, Weiner et al. disclose a method of using fluorescence correlation spectroscopy to measure levels of hepatitis C virus RNA, which is a macromolecule. The RNA of hepatitis C virus is not a pathogen. Weiner et al. also do not analyze the fluctuations in fluorescence due to the diffusion or flow of a pathogen through a subvolume. Rather, Weiner et al. analyze the diffusion of RNA. Weiner et al. thus fail to teach the method of claim 60. Accordingly, Applicants submit that the rejection of claim 59 under 35 U.S.C. § 102(b) over Weiner et al. has been overcome and respectfully request that it be withdrawn.

Claims 60, 61 and 66 are distinguishable under 35 U.S.C. § 102(b) over Weiner et al. for at least the same reasons set forth above in distinguishing claim 60.

Claims 59-62 and 65 stand rejected under 35 U.S.C. § 102(b) over Walter et al. (Proc. Natl. Acad. Sci., USA, November 1996, vol. 93, pp. 12805-12810).

Walter et al. discuss methods for combining an amplification technique, namely the PCR, with fluorescence correlation spectroscopy to detect the specific *in vitro* amplification of the genomic sequence of a bacterium. Walter et al. describe using at least one primer, a rhodamine-labeled fluorescent probe, and *Mycobacterium tuberculosis* genomic DNA as a target. Walter et al. disclose various combinations of primer/probe concentrations during PCR amplification of a target sequence specific for the *M. tuberculosis* sequence for effective products. Walter et al. also disclose the use of fluorescence correlation spectroscopy to measure the diffusion times of fluorescently labeled nucleic acids.

As set forth above, claim 59 is directed to a method of assaying for a pathogen in a sample that includes a least one pathogen, at least one probe, and at least one fluorescent tag. Walter et al. do not teach a sample that includes a pathogen. To the contrary, Walter et al. disclose combining an amplification technique, namely PCR, with an FCS-based detection technique and testing the method with different primer/probe combinations on *Mycobacterium tuberculosis* genomic DNA as a target. Walter et al., abstract. (Emphasis added.) The genomic DNA of *Mycobacterium tuberculosis* is not a pathogen. Walter et al. thus fail to teach a required element of the method of claim 59. Applicants submit therefore that the rejection of claim 59 under 35 U.S.C. § 102(b) over Walter et al. is unwarranted and respectfully request that it be withdrawn. Should this rejection be maintained, Applicants respectfully request that the next action indicate, by reference to page and line number, the location in Walter et al. of a teaching of a sample that includes a pathogen.

Claim 60 is now directed to a method of assaying for the presence of a pathogen in a sample where the method includes exciting a sample with radiation, the sample including at least one probe capable of binding a predetermined pathogen, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence that are due to the diffusion or flow of the pathogen through the subvolume, and determining the presence or absence of the pathogen. Walter et al. do not assay for the presence of a pathogen. Rather, Walter et al. analyze properties associated with probes bound to DNA. Walter et al. also do not teach analyzing fluctuations in fluorescence due to the diffusion or flow of a pathogen through a subvolume. Rather, Walter et al. analyze fluctuations in fluorescence associated with probes bound to various DNA. A DNA is not a pathogen. Walter et al. thus fail to teach the method of claim 60. Accordingly, the rejection of claim 60 under 35 U.S.C. § 102(b) over Walter et al. has been overcome and Applicants respectfully request that it be withdrawn.

Claims 61-62 and 65 are distinguishable under 35 U.S.C. § 102(b) over Walter et al. for at least the same reasons as set forth above in distinguishing claim 59.

Claims 59-66 stand rejected under 35 U.S.C. § 103 over Kask (US 6,515,289) in view of Lahiri et al., (US 2003/0138853 A1).

Kask discloses methods for detecting substances in a sample or to measure the interaction or reaction of these substances. Kask specifically describes a method of identifying nucleic acid strands by a labeled probe molecule. Kask explains using a mixture of primers labeled with dyes of different brightness to identify a target nucleic acid. Kask discloses monitoring intensity fluctuations of radiation emitted by the molecules or particles in at least one measurement volume, determining intermediate statistical data, and determining a distribution of molecules or particles as a function of at least two specific physical properties of the intermediate statistical data.

Lahiri et al. disclose an array that includes a plurality of biological membrane microspots on a surface of a substrate. The array can be produced, used, and stored in an environment that is exposed to air under either ambient or controlled humidity (Lahiri et al., Abstract). The method of Lahiri et al can be used for detecting a binding event between a probe array and target compounds (*Id.* at [0023]). Lahiri et al. explain that the array can be interfaced with optical detection methods (*Id.* at [0071]).

Claim 59 is now directed to a method of assaying for a pathogen in a sample. The method includes exciting a sample with radiation, measuring the fluorescence from a subvolume of the sample, and analyzing the fluctuations of the fluorescence. The sample includes a least one pathogen, at least one probe, and at least one fluorescent tag. In order to establish a *prima facie* case of obviousness, "the prior art reference (or references when combined) must teach or suggest all of the claim limitations." M.P.E.P. 2142. Kask discloses a method for characterizing a sample on the basis of intermediate statistical data. Kask mentions bacteria and viruses. Bacteria and viruses are not inherently pathogens. It is undisputed that Kask does not teach or suggest a method of assaying for a pathogen in a sample or a sample that includes a pathogen.

Lahiri et al. do not cure the deficiencies of Kask. The only mention Lahiri et al. make of a pathogen occurs at paragraph [0077] therein. In particular, Lahiri et al. disclose, "The array may be used in a diagnostic manner when the plurality of analytes being assayed are indicative of a disease condition or the presence of a pathogen in an organism." Lahiri et al., [0077]. (Emphasis added.) Lahiri et al. further disclose, "In such embodiments, the sample … [that] is delivered to the array will then typically be derived from a body fluid or a cellular extract from the organism." *Id.* The above-quoted

passages do not inherently constitute an express teaching of a sample that includes a pathogen. Lahiri et al. do not explain what is meant by "derived from" a body fluid. The term "derived from" does not inherently mean that the sample includes a pathogen. In addition, analytes that are indicative of the presence of a pathogen are not necessarily, i.e., inherently, pathogens. Rather, such analytes could be antibodies to the pathogen. Therefore, because neither Kask nor Kahiri et al. teach a sample that includes a pathogen, the proposed combination of Kask and Kahiri et al. lacks a required element of the method of claim 59. Applicants submit, therefore, that the rejection of claim 59 under 35 U.S.C. § 103 over Kask in view of Kahiri et al. has been overcome and respectfully request that it be withdrawn.

Claim 60 is now directed to a method of assaying for the presence of a pathogen in a sample where the method includes exciting a sample with radiation, the sample including at least one probe capable of binding a predetermined pathogen, and at least one fluorescent tag, measuring the fluorescence from a subvolume of the excited sample, analyzing the fluctuations of the fluorescence that are due to the diffusion or flow of the pathogen through the subvolume, and determining the presence or absence of the pathogen. Neither Kask nor Kahiri et al. teach or suggest analyzing fluctuations of fluorescence due to the diffusion or flow of pathogen through a subvolume. The proposed combination of Kask and Kahiri et al. thus lacks a required element of claim 60. Applicants submit, therefore, that the rejection of claim 60 under 35 U.S.C. § 103 over Kask in view of Kahiri et al. has been overcome and respectfully request that it be withdrawn.

Claims 61-66 are distinguishable under 35 U.S.C. § 103 over Kask in view of Lahiri et al. for at least the same reasons as set forth above in distinguishing claim 60.

The claims now pending in the application are in condition for allowance and such action is respectfully requested. The Examiner is invited to telephone the undersigned should a teleconference interview facilitate prosecution of the application.

Please charge any additional fees that may be required or credit any overpayment made to Deposit Account No. 501,171.

Respectfully submitted,

Date: October 23, 2006

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Sheet 1 of 3

Substitute form PTO-1449 (Modified) U.S. Department of Commerce	Attorney Docket No. 205-007US2	Application No. 10/632,725
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Applicant David E. Wolf et al.	
(37 C.F.R. §1.98(b))	Filing Date August 1, 2003	Group Art Unit 1743

U.S. PATENT DOCUMENTS

Examiner Initials	I.D.	Patent Number	Issue Date	Patentee	Class	Sub Class	Filing Date if Appropriate
MS	AA	6,203,994	03/20/01	Epps et al.			
	AB	4,868,103	09/19/89	Stavrianopoulos, et al.	435	5	
	AC	5,439,797	08/08/95	Tsien, et al.	435	7.21	
	AD	5,998,204	12/07/99	Tsien, et al.	435	326	
	AE	6,291,201	09/18/01	Garman	435	23	
	AF						
	AG						

FOREIGN PATENT DOCUMENTS OR PUBLISHED FOREIGN PATENT APPLICATIONS

Examiner Initials	ID	Document Number	Publication Date	Country or Patent Office	Class	Sub Class	Translation Yes	Translation No
MS	AH	WO 01/55452	08/02/01	PCT				
	AI							
	AJ							

OTHER DOCUMENTS (INCLUDE AUTHOR, TITLE, DATE AND PLACE OF PUBLICATION)

Examiner Initials	ID	Document
MS	AK	Doi, N., "Novel fluorescence labeling and high-throughput assay technologies for in vitro analysis of protein interactions," Genome Research, www.genome.org, vol. 12, pages 487-492 (Feb. 2002).
	AL	Lam, K.S. et al., "Synthesis of One-Bead One-Compound Combinatorial Peptide Library," *Methods in Molecular Biology*, vol. 87: 20 (1-6) Combinatorial Peptide Library Protocols (S. Cabilly, Humana Press Inc., Totowa, NJ (1998).
	AM	Johnsson, K. et al., "Phage Display of Combinatorial Peptide and Protein Libraries and Their Applications in Biology and Chemistry," Combinatorial Chemistry in Biology (M. Famulok et al. Eds) pages 87-105 (1999).

Examiner Signature	Date Considered
/Mark Shibuya/	07/13/2006

EXAMINER: Initial citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Disclosure form (PTO-1449)